Cannabinoids, cannabis, and cannabis-based medicines for pain management: an overview of systematic reviews

R Andrew Moore (DSc)[1] Emma Fisher (PhD),[2,3] David P. Finn (PhD) [4] Nanna B Finnerup (M.D.),[5] Ian Gilron (MD),[6-8] Simon Haroutounian (PhD),[9] Elliot Krane (MD), [10] Andrew SC Rice (MD),[11] Michael Rowbotham (MD),[12,13] Mark Wallace (MD)[14], Christopher Eccleston (PhD) [2,3,15]

**Corresponding author:* Andrew Moore [andrew.moore@omkltd.org]

[1]Court Road, Newton Ferrers, Plymouth, U.K.

[2]Centre for Pain Research, University of Bath, Bath, UK

[3]Cochrane Pain, Palliative, and Supportive Care Review Groups, Oxford University Hospitals, Oxford, UK

[4]Pharmacology and Therapeutics, School of Medicine, Galway Neuroscience Centre and Centre for Pain Research, NCBES, Human Biology Building, National University of Ireland Galway, University Road, Galway, Ireland.

[5]Danish Pain Research Center, Department of Clinical Medicine, Aarhus University, and Department of Neurology, Aarhus University Hospital, Aarhus, Denmark.

[6]Department of Anesthesiology & Perioperative Medicine, Kingston General Hospital and Queen's University, Kingston, ON, Canada;

[7]Centre for Neuroscience Studies, Queen's University, Kingston, ON, Canada;

[8]School of Policy Studies, Queen's University, Kingston, ON, Canada;

[9]Division of Clinical and Translational Research and Washington University Pain Center. Department of Anesthesiology, Washington University School of Medicine. St Louis, MO, USA

[10]Department of Anesthesiology, Perioperative and Pain Medicine, & Pediatrics, Stanford University School of Medicine, Stanford, Palo Alto, California, USA.
[11]Pain Research, Department of Surgery & Cancer, Faculty of Medicine, Imperial College London, UK
[12]Department of Anesthesia, Pain Management Center, University of California San Francisco.
[13]Sutter Health, CPMC Research Institute, California Pacific Medical Center Research Institute, California, USA
[14]Division of Pain Medicine, Department of Anesthesiology, University of California San Diego.
[15]Department of Clinical and Health Psychology, Ghent University, Ghent, Belgium.

Abstract

Cannabinoids, cannabis and cannabis-based medicines (CBM) are increasingly used to manage pain, with limited understanding of their efficacy and safety. We assessed methodological quality, scope, and results of systematic reviews of randomised controlled trials (RCTs) of these treatments. Several search strategies sought self-declared systematic reviews. Methodological quality was assessed using both AMSTAR-2 and techniques important for bias reduction in pain studies. Of 106 papers read, 57 were self-declared systematic reviews, most published since 2010. They included any type of cannabinoid, cannabis, or CBM, at any dose, however administered, in a broad range of pain conditions. No review examined the effects of a particular cannabinoid, at a particular dose, using a particular route of administration, for a particular pain condition, reporting a particular analgesic outcome.

Confidence in the results in the systematic reviews using AMSTAR-2 definitions was critically low (41), low (8), moderate (6), or high (2). Few used criteria important for bias reduction in pain. Cochrane reviews typically provided higher confidence; all industry-conflicted reviews provided critically low confidence. Meta-analyses typically pooled widely disparate studies, and, where assessable, were subject to potential publication bias. Systematic reviews with positive or negative recommendation for use of cannabinoids, cannabis, or CBM in pain typically rated critically low or low (24/25 [96%] positive; 10/12 [83%] negative).

Current reviews are mostly lacking in quality and cannot provide a basis for decision-making. A new high-quality systematic review of RCTs is needed to critically assess the clinical evidence for cannabinoids, cannabis or CBM in pain.

Summary

Available systematic reviews are of insufficient quality adequately to assess the evidence of cannabinoids, cannabis, and cannabis-based medicines for use in pain management.

1 Introduction

In 2018 the International Association for Study of Pain established a Task Force on the use of cannabinoids, cannabis, and cannabis-based medicines (CBM) for pain management. It has four Work Packages (WP) focused on 1) basic science and evidence for efficacy in preclinical models [72], 2) evidence for clinical analgesic efficacy [28] 3) risk and evidence of harm to the individual [31,50], and 4) the societal impact and policy.

This overview review is part of the second WP and is focused on summarizing the evidence of efficacy presented in systematic reviews of randomized controlled trials (RCTs) of any broadly-defined cannabinoid product in any type of pain condition.

There have long been concerns about the quality of most of the medical literature [37,68]. A 1996 survey indicated that 90% of meta-analyses had methodological flaws that could limit their validity, and that meta-analyses of low quality produced significantly more positive conclusions [39]. There has subsequently been an epidemic of systematic reviews, with huge growth rates in their numbers without any necessary improvement in their quality [68], leading to the conclusion that the large majority of systematic reviews and meta-analyses are unnecessary, misleading, and/or conflicted. Industry-

supported meta-analyses have been found to be less transparent, with few reservations about methodological limitations of the included trials, and with more favourable conclusions than corresponding Cochrane reviews [41].

Even in good quality Cochrane reviews, the use of Grading of Recommendations Assessment, Development and Evaluation (GRADE) to summarise the quality of evidence indicates that fewer than 20% of reviews actually have any high quality evidence [30]. Only confusion results from the product of low quality evidence and low quality systematic review of that evidence. High standards in clinical trials and systematic reviews of those trials are absolutely essential to improve knowledge, make policy, or make individual clinical decisions; anything else is guesswork.

The aim of this overview review of WP2 was therefore to assess the methodological quality, scope, reported results of systematic reviews and meta-analyses of RCTs of cannabinoids, cannabis, and CBM for pain relief, and to determine whether any new systematic review was required.

2 Methods

A protocol for this overview is registered on Prospero (Prospero ID CRD42019124710) and published [28]. We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols [49]. A truncated report of methods is therefore given here.

2.1 Systematic reviews for inclusion

We chose to include any review whose authors defined as a systematic review of RCTs, although definitions of what comprises a systematic review are

considerably more restrictive [34]. The intention in the protocol was to analyse only high quality evidence found in Cochrane Effective Practice and Organisation of Care [25] GRADEs of evidence as high or moderate quality, though in the event this was not possible.

2.2 Participants

We included systematic reviews of RCTs involving people of any age with any form of acute and chronic pain, including pain secondary to another condition, such as pain with spasm, multiple sclerosis (MS), or leg cramps. Experimental pain was not included.

2.3 Interventions and comparators

We included any type of cannabinoid product (natural or synthetic), cannabis, or CBM, by any route of administration, at any dose, and with any comparison intervention. This included endocannabinoid system modulators such as fatty acid amide hydrolase (FAAH) inhibitors and *N*-paltmitoylethanolamide (PEA). For inclusion, systematic reviews were required to examine interventions to reduce pain intensity.

2.4 Outcomes

A range of primary and secondary outcomes were proposed in the protocol. The limited nature of systematic reviews included meant that this overview was restricted to measures of analgesic efficacy only.

2.5 Search and selection of systematic reviews

We searched PubMed, EMBASE, DARE, and the Cochrane Controlled Register of Trials (CENTRAL) for systematic reviews of cannabinoids, cannabis, and CBM and for people with pain. The main search was completed in August 2019. Bibliographies of included and excluded reviews were examined for possible reviews, and electronic citations of PubMed and Google Scholar also examined. We conducted targeted searches for further systematic reviews through additional electronic searches, through reference lists of retrieved articles and reviews, or through other sources up to January 2020. Two authors independently sifted the titles and abstracts identified, with a third author resolving disagreement.

2.6 Data extraction

Data extraction was conducted by two authors (RAM & EF) and checked by others; disagreement was resolved by consensus (initially discussion with CE, but wider if needed). The following information was extracted from each review:

1. Review characteristics, e.g., design, participants, age and sex, pain condition, inclusion/exclusion criteria, risk of bias method. In addition, we sought information related to Assessment of Multiple Systematic Reviews (AMSTAR)-2 [67], methodological issues related to known sources of bias in pain studies, use of GRADE, and GRADE assessment if used. We extracted the number of trials and patients used in assessment of pain, the number in randomised trials, and the number in randomised trials used to calculate any summary estimate of analgesic efficacy.

2. Intervention and comparator characteristics, e.g., type of cannabinoid, dose, route of administration, comparator.
3. Outcomes listed in the primary outcomes.

In addition, we made a judgement on the strength of any recommendation made by authors in the review abstract. This was done by RAM and EF, discussed initially with CE, and then wider if needed. Judgements were based on being positive (recommended use), equipoise (a balance of evidence), or negative (recommended non-use), or no statement. Strength was judged as strong (e.g. provide reasonable therapeutic option, should not be used), moderate (e.g. moderately effective, no unbiased evidence), or weak (e.g. small analgesic benefit, more trials needed to support).

2.7 Assessment of review quality and validity

We assessed each included review using AMSTAR-2 [67]. Two authors assessed each review using the criteria with disagreement resolved by consensus.

We also conducted additional validity checks of potential critical importance in the evaluation of analgesic efficacy. These included:

- Did the review use a defined diagnostic criterion for pain conditions?
- Did the reviews include only studies in which patients made their own assessment of pain? (professional and patient assessment often disagrees, with professionals significantly underestimating pain [66]).
- Did the reviews use studies with defined minimum pain intensity of moderate or severe pain? (mild pain can reduce the sensitivity of trials to demonstrate an analgesic effect).

- Did the reviews examine study size as a confounding factor in any analysis of efficacy? (systematic reviews have been criticised for being over-confident of results with inadequate data [2,65,79]; there is increasing evidence of the importance of small trial size, both because of random chance [16,52,76], and as an important source of bias [22,23,26,36,57].
- Did the review examine susceptibility to publication bias? (if possible, for each review with dichotomous numerical data we will assess the likelihood of publication bias [51]).

2.8 Data synthesis and/or descriptive evaluation of reviews

We planned to evaluate strengths and weaknesses of systematic reviews of cannabinoids in treating pain by a descriptive analysis, and meta-analysis if appropriate. As there was little high quality evidence found, and none useable for meta-analysis, the descriptive analysis of all systematic reviews became the only mechanism of evaluation.

The absence of combinable data did not preclude unplanned evaluations, including links between AMSTAR-2 score matched critical methodological criteria for evaluation of analgesic efficacy, the potential impact of reviews using Google Scholar citation numbers, judgement on the strength of recommendations by review authors based on language in the abstracts, numerical assessment of analgesic efficacy, and how these factors interacted.

The nature of the reviews precluded any useful independent assessment of GRADE for individual reviews.

3 Results

3.1 Results of search

Initial electronic searching found 685 possible systematic reviews, reduced to 559 after removal of duplicates. After reading the abstracts 106 papers were obtained in full, and read for possible inclusion as a systematic review. Forty-nine were excluded (Appendix 1 lists the reasons and references). Reasons for exclusions were:

- 12 were narrative or scoping reviews;
- 11 were practice guidelines, position papers, or therapeutic recommendations;
- 8 were overview reviews;
- 2 each were not systematic reviews, had no pain outcomes; did not investigate cannabinoids, were duplicates, were older versions of updated systematic reviews, or were thesis chapters not relevant to this overview;
- 1 each was a clinical trial, a review of consensus statements, investigated placebo only, investigated experimental pain, investigated adverse events, or investigated combination therapies without cannabinoids alone.

Fifty-seven [3,5-15,17,19-21,24,27,29,32,33,35,38,40,42-48,54-56,58-64,69-71,73-75,77,78,80-87] were included in this overview review as systematic reviews investigating cannabinoids, cannabis, or CBM in RCTS with pain as an outcome (Appendix 2 gives information on date of publication, pain or other condition examined, type of CBM investigated, route of administration, and abstract conclusion). Seven were Cochrane reviews [5,10,15,54,59,64,82], and

six reported either financial sponsorship from a pharmaceutical company or were conflicted because authors were employees of a company with interests in cannabinoids [8,38,46,69,70,71].

Forty-seven reviews specifically examined pain (10 neuropathic pain, 10 any type of pain, 8 chronic non-cancer pain, 7 cancer pain, 4 rheumatic pain, 2 fibromyalgia, 2 spinal cord injury, 1 acute pain, 1 pain in children, 1 HIV neuropathy, and 1 phantom limb pain). Ten reviews considered conditions in which pain was one of several symptoms (5 muscular dystrophy, 3 neurological conditions, 1 leg cramps, and 1 gastrointestinal conditions).

3.2 General description of included studies

Included studies were mostly published recently. The earliest was published in 2001 [17] and the most recent in 2019 [13,33,56,63,86]. Only five were published before 2010; most (90%) were published since 2010 (Figure 1), and two-thirds of the included reviews had been published in the past five years

Summary information on these 57 systematic reviews is shown in Table 1, organised by pain condition. As several of these systematic reviews examined a wide range of medical conditions, only the information involving pain and cannabinoids is shown.

Neuropathic pain, chronic non-cancer pain, all pain, and cancer pain predominated, but 15 distinct areas were recognised. Some were not classic pain conditions, for example pain associated with spasm in MS or leg cramps.

The number of studies and patients involved, the number of randomised trials included, and the number available for any statistical analysis varied widely

between reviews and pain conditions. For six pain conditions there were no available data for analysis. Some reviews in some conditions analysed data from several thousand patients. For example, Yanes et al [86] analysed data from 25 trials and 2,248 patients in a meta-regression for all pain conditions, and Torres-Moreno et al [77] pooled data from 2,692 patients in 11 MS trials. The variation in numbers between reviews in apparently the same condition reflected different approaches in analysing drug and formulation, route of administration, and whether a broad or narrow approach to type of condition was used (for example, painful diabetic neuropathy rather than all neuropathic pain).

Risk of bias was assessed in 45 of the 57 reviews, predominantly using Cochrane risk of bias tools (27), the Oxford quality scale (13) or a modification of it (3), an American Academy of Neurology tool (1) or a Physiotherapy Evidence Database tool (1). Twelve systematic reviews made no apparent mention of formal risk of bias assessment [8,11,12,20,42,60,62,78,80,85-87].

3.3 Cannabinoid used and route of administration

Reviews examined the effects of a wide range of cannabinoid drugs or preparations, though these were seldom clearly defined. The most common definition was 'cannabinoid' in 36 reviews, 'any cannabis preparation' in eight, 'plant-based cannabis preparation' in six, two each examined nabilone, dronabinol, or nabiximols, two PEA derivatives, and one each Δ^9-tetrahydrocannabinol (THC), cannabidiol, and *Cannabis sativa*. Appendix 3 shows their use by pain condition.

Route of administration was generally not defined (36 reviews), or 'any route' (15 reviews), oral or topical (4 reviews), or smoked or inhaled (2 reviews) (Appendix 4).

3.4 Pain outcome used in systematic reviews

Few reviews clearly defined an outcome of at least 30% or 50% pain intensity reduction considered by patients to be a good outcome [53](Appendix 5 for results according to pain condition); only 14 reviews (25%) sought these outcomes. Most, 28 reviews, did not define an outcome. The remaining reviews used some calculation based on continuous variables, mostly standardised mean difference or mean difference (10 reviews), effect size (3 reviews), or other (2 reviews). Three-quarters of the reviews therefore made no prior adjudication of what a successful outcome might be or justified the choice of outcome.

3.5 Use of GRADE

GRADE evaluation of overall evidence certainty was used in 17 systematic reviews, and not used in 40. Of the 17 that used GRADE, 13/17 (76%) included very low certainty; the ratings were:

0 high certainty,
4 moderate certainty,
1 moderate or very low certainty,
3 low certainty,
2 low or very low certainty,
7 very low certainty.

3.6 AMSTAR rating

Each review was judged according to the 16-criterion AMSTAR 2 list; Appendix 6 shows scoring for individual reviews. The results (Table 2) showed that only four of the criteria were met by more than half of the reviews (showing some detail of included studies (85%), conflict of interest reporting (81%), study selection in duplicate (65%), and data extraction in duplicate (56%)).

Meeting some criteria was not applicable. For example, as many reviews had few studies, with those studies often small and clinically heterogeneous, no meta-analysis was appropriate. That situation made it difficult to discuss risk of bias or heterogeneity on the result. It was also difficult to judge whether risk of bias was satisfactory. In addition, the AMSTAR criterion for a comprehensive literature search demanded searches of grey literature, consulting experts in the field, and searching of trial registries. One review met all those criteria [13], and 53 reviews partially met the criteria for a literature search, typically not searching grey literature.

Other criteria met uncommonly were a study design explanation (no reviews), reporting on sources of funding of studies (19 reviews), production of a complete PICO (Patient, Intervention, Comparison, Outcome; 13 reviews), assessment of small study bias (14 reviews), and prior publication of a protocol (17 reviews).

The failure to meet critical and non-critical AMSTAR criteria resulted in generally low assessments of overall confidence in the results of the review. Using the AMSTAR definitions, confidence in the results of 86% of the reviews was critically low (41 reviews) or low (8 reviews). For six reviews was confidence in the results moderate, and for only two was it high; only 1 in 7 systematic reviews had moderate or high AMSTAR confidence.

For the seven Cochrane reviews overall confidence was high or moderate in four, and low in three; none was critically low. All six conflicted reviews were assessed as having critically low confidence (Figure 2). Of the 12 reviews not specific for pain, nine were evaluated as critically low, and three of low confidence.

Appendix 7 shows AMSTAR confidence assessments in the results of the reviews according to the pain condition investigated.

3.7 Use of critical criteria for assessment of analgesic efficacy

Because AMSTAR is a generic instrument not specifically designed for use with analgesic studies, we also assessed the systematic reviews for the use of methodologies designed to avoid significant biases in pain trials (Appendix 6 for individual result scoring and Appendix 8 for summary results by pain condition). The results for this assessment demonstrated that methods used to minimise bias in analgesic studies were typically not used (Figure 3).

Only half of the reviews specified using trials that were both properly randomised and properly double blind. About 10% or fewer required patient reported pain only, performed any sensitivity analysis for small trials, evaluated sensitivity of a result to publication bias, used studies where entrants were required to have pain with a minimum pain intensity, or evaluated the potential impact of imputation method for missing data.

Results for the seven Cochrane reviews overall confidence were mixed. Three from a pain-specific group used only randomised and double blind studies and met 50% or more of the criteria. The other four accepted studies that were not necessarily randomised or double blind and met 25% of criteria or

fewer. Four of the six conflicted reviews used only randomised and double blind studies and met 38% or fewer of the criteria. Of the 12 reviews not specific for pain, only four used randomised and double blind studies and 11 met 25% or fewer of the criteria.

3.8 Concordance between AMSTAR and critical pain criteria

Thirty-seven of the 39 (95%) reviews with AMSTAR ratings of critically low met two or fewer of the eight critical pain criteria compared with 5/8 (63%) rated low, and 2/7 (29%) of those rated moderate or high. There was a tendency for higher scores in reviews with AMSTAR rating of moderate or high (Table 3).

A few individual reviews stood out against the trend. For example, Finnerup et al [27] had a critically low AMSTAR rating, but met six of eight critical pain criteria, while Brettshneider et al [15] had a high AMSTAR rating but scored only one of eight criteria. Results of the three Cochrane reviews from a pain-specific group scored reasonably well on both.

3.9 Impact of systematic reviews

We examined the impact of the 54 of the 57 systematic reviews by looking at the number of citations for each as reported by Google Scholar on Sept 20 2019; three 2019 publications were identified after that date, and would have had few if any citations. The 54 reviews had been cited a total of 6760 times (mean 125 citations, median 47 citations), with about 1100 citations a year (mean 22 citations a year, median 9 citations a year).

The majority of citations came for a small number of systematic reviews (Figure 4). Two reviews were cited on average over 200 times a year [27,84], and three other reviews were cited between 50 and 100 times a year [5,42,54]. Because most reviews had been published within a limited period, no effect of recency in citation rate was discernible.

There was no consistency as why these five were particularly heavily cited. Table 4 summarises information on these reviews, with possible reasons for their high citation rate.

3.10 Judgement on abstract strength of recommendation

Abstracts of systematic reviews typically provide some comment on the strength of evidence or the direction of any effect, and frequently both. These can be interpreted as recommendations or are frequently framed as recommendations. We made a judgement as to whether the implied recommendation in an abstract was positive or negative (strong, moderate, or weak), or showed equipoise, or whether there was no recommendation relating to the use of cannabinoid-based medicines for treatment of pain. Table 5 shows examples of how we made these judgements, with details of each in Appendix 7.

Of the 44 systematic reviews making a recommendation, 27 were moderate or strong, 10 weak, and 7 indicated equipoise. Of the seven Cochrane reviews, three had no opinion, two were strong negative, one at equipoise, and one was weak positive. Of the six conflicted reviews, three had no opinion, one was weak positive, and two were strong positive. Eight of the 19 reviews with moderate or strong positive recommendation had no formal risk of bias

assessment [8,11,12,20,42,60,61,86]. All reviews making weak recommendations had a risk of bias assessment.

3.11 Relationship between abstract strength of recommendation, AMSTAR rating, and critical pain criteria

Table 6 shows the AMSTAR rating and critical pain criteria score. Systematic reviews with any positive recommendation of use of cannabinoids, cannabis, or CBM in pain typically rated critically low on AMSTAR (20/25; 80%) or critically low or low (24/25; 96%). They typically used two or fewer of the eight critical pain criteria to avoid bias. Reviews with negative recommendations were somewhat less likely to have a critically low (6/12; 50%) or critically low or low rating (10/12; 83%), and used three or more critical pain criteria.

Reviews making weak positive or negative recommendations were more likely to use more critical pain criteria than those making moderate or strong recommendations.

3.12 Calculation of magnitude of analgesic effect

Seventeen systematic reviews used numeric data to calculate the magnitude of any analgesic effect, for a variety of interventions, routes of administration, and painful condition, using a range of different pain outcomes and statistical outputs (Table 7). Analyses were conducted on data sets that varied between 1 and 25 trials, and 22 and 2692 patients. No analysis was conducted on a defined intervention, defined dose or intensity, or defined route of administration in a defined pain condition.

Ten of 18 reported results showed statistical difference from placebo, while 8 showed no difference. Statistical significance was associated with positive abstract recommendation, while no significance was associated with negative abstract recommendations.

Table 7 also shows AMSTAR-2 confidence level and the number of points scored for critical pain elements. Statistical significance was generally associated with critically low AMSTAR assessment and 3/8 or fewer pain criteria. The exception was a review of short-term (six hours to five days) effects of inhaled or smoked cannabis in small number of patients with chronic pain conditions in trials with significant risk of bias [7].

Reviews without statistical significance generally made no recommendation or a negative recommendation, with a tendency to higher AMSTAR grades and higher scores for critical pain elements. Exceptions were Stockings et al [74] with bare significance for one outcome, and Phillips et al [61] which included only 89 patients.

A calculation of the susceptibility to publication bias from studies with null results was based on an NNT of 10 or greater being clinically not relevant [51]. No calculation was possible where there was no statistical significance (NNT is then essentially infinity), or for reviews reporting continuous outcomes. For only three of these reviews were data available that allowed for the calculation. The number of people in trials with null results required to overturn the statistically significant results for cannabinoids was 213 in Nugent et al [58], 237 in Phillips et al [61], and 145 in Andreae et al [7].

4 Discussion

To the extent that any conclusions can be drawn from existing systematic reviews, they can only be made with respect to the types of cannabinoid, cannabis, and CBM investigated to date, in the specific patient groups and pain types studied. No conclusions with respect to other interventions yet to be tested are possible.

Of the many reviews of the effects on pain of studies concerning cannabinoids, cannabis, and CBM published to the end of 2019, 57 claimed to be systematic reviews. The Cochrane Handbook lists five key characteristics of a systematic review [34]: a clearly stated set of objectives, explicit and reproducible methods, systematic and comprehensive searches, assessment of validity of results including risk of bias, and a systematic presentation of those results. While relatively few of the 57 systematic reviews examined here would meet these criteria, the cachet of a review claiming to be systematic is such that all required examination.

Included reviews examined 15 distinct pain areas. Most accepted any type of cannabinoid, at any dose, by any route of administration, though some had a more defined scope. No review examined the effects of a particular cannabinoid, at a particular dose or dose range, given by a particular route of administration, for a particular pain condition, and reporting a particular analgesic outcome.

The degree of pooling for any effect calculations could be extreme; for example, one review of cannabinoids in chronic pain pooled data from trials as short as six hours, and as long as 15 weeks [57]. Almost 80% of the reviews failed to define what a successful outcome might be; rather than defining a measure that is important to patients [54], the approach was to make important that which had been measured.

Judging systematic review quality is difficult. Most often used methodology is AMSTAR, and we used the most recent version, AMSTAR-2 [67]. This is a generic tool examining what is regarded as best practice in systematic review methodology. The 16 items are themselves not controversial, though judging whether a review meets a particular criterion is often subjective, open to disagreement between assessors because details of methods may be omitted from publications for reason of space. An AMSTAR-2 score probably represents a "worst case". No single criterion was met by more than 50% of the reviews, and confidence in the results of 86% of the reviews was critically low (41 reviews) or low (8 reviews). This is similar to an assessment of systematic reviews in back pain where 74% rated critically low and 16% low [4].

A generic approach to quality is of limited value in assessing analgesic effects, because it does not examine criteria known to be associated with considerable bias in pain trials. We examined eight of those with established association with risk of bias, and again few reviews used them. Randomisation and blinding were defined criteria in just over half of the reviews, but five of the eight criteria were used by 10% or fewer of the reviews. Reviews with low AMSTAR-2 rating typically used few pain-associated risks of bias, while those providing moderate or high confidence used more.

The implication is that significant sources of potential bias were likely to have affected results from most of the 57 systematic reviews. Cochrane reviews tended to be better, especially more recent reviews, while conflicted systematic reviews with pharmaceutical company backing were poor.

Quality was not associated with the impact of reviews as judged by annual citation rates on Google Scholar. Three of the top five cited reviews met many pain criteria (though not necessarily AMSTAR); the strength of recommendation in the abstracts of these reviews was weak negative or none. Two were rated critically low confidence by AMSTAR and used very few important criteria for avoiding bias in pain studies and reviews (Table 4); their strength of recommendation was moderately or strongly positive.

Of the 17 reviews attempting a numerical calculation of the magnitude of the analgesic effect, nine had a positive and five a negative recommendation. Reviews with positive recommendations were associated with a statistically significant analgesic effect, but not reviews with negative or no recommendation. Susceptibility to publication bias for three reviews with statistical significance showed that the result would have been overturned by a null result from a clinical trial of 100-250 patients. Moreover, eight of 19 reviews with moderate or strong positive assessment, statistical significance or no, did not evaluate risk of bias, whereas all making a negative recommendation assessed risk of bias.

To summarise, what we have is a body of work that tells us little about whether any particular cannabinoid or cannabis-based treatment tested to date, at a particular dose and route of administration, given to someone with a particular form of pain could lead to a particular degree of pain reduction (at least 50% pain intensity reduction or reduction of pain to just mild [54]). Low quality reviews do no more than suggest there may be, while the highest quality say probably not.

It is telling that a US National Academies of Sciences, Engineering and Medicine report on therapeutic effects of cannabis and cannabinoids, and a

later update [1,18], concluded that there is "substantial" evidence that cannabis is an effective treatment for chronic pain in adults. The committee included experts in substance abuse, cardiovascular health, epidemiology, immunology, pharmacology, pulmonary health, neurodevelopment, oncology, pediatrics, public health, and systematic review methodology, but not pain. It based much of its findings on pain on the systematic review of Whiting et al [34]. That review was given an AMSTAR rating of critically low confidence and used only 2/8 pain methodologies. Moreover, for the patient-orientated outcome of at least 30% pain intensity reduction it reported a result not significantly different from placebo, including, as it did, no significant difference in the 95% confidence interval (odds ratio 1.41 (0.99 to 2.00)). That conclusion should be revisited, revised, or retracted, as it is significantly misleading.

There are several lessons:

1. The label of systematic review does not itself confer value for pain. Generic scoring systems for systematic reviews provide limited confidence, and the best mechanism to ensure that a systematic review provides a robust and reliable answer is to combine generic Cochrane approaches with pain specific criteria, as several Cochrane review groups do. Systematic reviews of cannabinoids, cannabis, and CBM in pain require authors skilled not only in systematic review methodology but also those knowledgeable about pain and cannabinoids.
2. Clinical trials to measure analgesic effect have a long-established basic methodology, but recent decades have demonstrated additional situation-specific factors needing consideration. Trials need to be conducted to the highest standards (especially those for registration or

marketing purposes) and provide outcomes of clinical as well as statistical relevance to both efficacy and harms.

3. RCTs investigating cannabis, cannabinoids, and CBM and pain should be designed to include well-defined populations with specific pain diagnoses, evaluate particular interventions (specific cannabinoid, doses, route of administration) and comparators, and report on meaningful patient reported pain outcomes (including functional outcomes and not just analgesic efficacy). Good RCTs can be complemented by patient registries to gather data on long-term patient outcomes to explore effectiveness of cannabinoids, cannabis and CBMs for the treatment of pain and function in real life.
4. More details of the clinical trials should be provided in reviews, particularly relating to concomitant analgesic medication, previous use of cannabinoids and other analgesics, and whether testing has been conducted to exclude non-trial use of drugs in test or placebo arms.
5. The fact that on AMSTAR-2 alone, 41 systematic reviews providing critically low confidence in their results were published in medical journals (including some prestigious journals) indicates a potential problem with research quality. It is debatable whether this is a failure of journals and the peer review system, or whether scoring systems are unrealistic and penalise reviews unnecessary. Does a literature search of grey literature actually improve systematic reviews of RCTS, for example?
6. Low quality and over-claiming positive benefits have long been associated [37,39]. There is no obvious sign of improvement, and that is a matter of considerable concern.
7. The link between the low quality of reviews and the positive or negative assessment of analgesic efficacy in review abstracts (often the only part that is read in any detail, or at all) is of concern. It begs the question

not of challenge to these reviews, but to whether the implications are such as to consider calls for retraction. A Cochrane review compromised by methodological faults would likely be retracted, perhaps the only situation in which that would happen.

Conclusion

The primary reasons for this overview review were to examine the quality of the extant review literature and question whether a new systematic review would be needed. The results of the overview demonstrate that most reviews are lacking in quality and cannot provide a basis for decision making. In the circumstances, a new systematic review adhering strictly to methodological requirements of AMSTAR and pain studies is required.

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Conflict of interests

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- Andrew Rice – Prof. Rice is a Council Member of IASP and Chair of the Presidential Task Force of the IASP, He undertook consultancy and advisory board work for Imperial College Consultants- in the last 24 months this has included personally remunerated work outside of the submitted work for: Pharmanovo, Lateral, Novartis, Pharmaleads, Mundipharma, Orion, Toray, Abide, Asahi Kasei & Theranexis. He was the owner of share options in Spinifex Pharmaceuticals from which personal benefit accrued between 2015 and 2019 upon the acquisition

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- Mark Wallace - Dr. Wallace reports personal fees from Insys, outside the submitted work.

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Figure legends

Figure 1: Rate of publication of 54 included systematic reviews

Number of systematic reviews on cannabinoids, cannabis, or CBM published each year between 2001 and 2019. No systematic review was published before 2001.

Figure 2: AMSTAR evaluation of confidence in results of systematic reviews

AMSTAR-2 evaluations as percentages of 57 systematic reviews, seven Cochrane reviews, and six conflicted reviews with industry sponsorship

Figure 3: Percentage use of criteria designed to minimise bias in analgesic trials

Percentage of reviews using criteria designed to minimise bias in analgesic trials (LOCF: last observation carried forward; BOCF: baseline observation carried forward)

Figure 4: Distribution of total citations and total publications according to annual rate of citation

Distribution of the percentage of total citations and total reviews according to the average number of citations per year for each review calculated from the number of Google Scholar citations divided by the number of years since

publication. A small percentage of reviews accounted for the largest percentage of citations